Current concepts of low testosterone levels in ageing men

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Low testosterone levels are associated with increased risk of cardiovascular disease and increased mortality in ageing men. Men with pathologically based hypogonadism should be considered for testosterone supplementation. For older men suspected of being androgen deficient in the absence of pituitary or testicular disease, controversy exists because symptoms can be nonspecific, the definition of low testosterone levels is under debate and the risks of extended treatment are uncertain.

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Testosterone is the primary male sex hormone or androgen in men. Hypothalamic secretion of gonadotrophin-releasing hormone (GnRH) regulates pituitary secretion of luteinising hormone (LH), which in turn stimulates testicular secretion of testosterone (see Figure). Testosterone regulates male sexual development, virilisation and body composition. There is considerable interest in the putative relation of low endogenous testosterone levels to risk of cardiovascular disease and increased mortality in ageing men.

Men who have an identifiable lesion within the hypothalamo-pituitary-gonadal axis, such as a pituitary tumour (or previous surgery or radiotherapy to the pituitary) or a primary testicular disorder, such as Klinefelter's syndrome, trauma, cytotoxic chemotherapy or orchitis, may exhibit pathologically based hypogonadism with a sound rationale for consideration of testosterone supplementation. Controversy arises over the definition of low testosterone levels in older men without pituitary or testicular disease, particularly in the context of non-specific symptoms and limited outcome data from randomised controlled trials.

Assessment of hypogonadal men

Symptoms and signs of androgen deficiency include reduced libido, decreased spontaneous erections, loss of body hair and reduced need for shaving, gynaecomastia and increased risk of osteoporosis or fracture.[1] Less specific symptoms and signs include decreased energy, motivation and self-confidence, lower mood, mild anaemia, reduced muscle bulk and increased body fat.

Testicular volumes can be assessed using an orchidometer. Men with hypothalamic or pituitary disease have normal or low LH and low testosterone levels (secondary hypogonadism), whereas those with testicular disease have elevated LH and low testosterone levels (primary hypogonadism). Therefore, biochemical evaluation should include measurement of circulating testosterone and LH levels. Sex hormone-binding globulin (SHBG) levels can also be measured because testosterone levels may be influenced by very low or very high SHBG levels. Obesity is associated with decreased SHBG concentrations,[1] and calculated free testosterone levels can be normal when total testosterone levels are low in the setting of low SHBG levels. Hyperprolactinaemia results in secondary hypogonadism responsive to dopamine agonist therapy.

Measurement of testosterone levels should be made using early morning blood samples to minimise confounding from circadian variation, preferably with a testosterone assay using mass spectrometry rather than the less accurate immunoassay.[2]

Key points

- **Men who have an identifiable lesion of the hypothalamo-pituitary-gonadal axis or a primary testicular disorder may exhibit pathologically based hypogonadism. These men should be considered for testosterone supplementation.**
- **Symptoms and signs of androgen deficiency include reduced libido, decreased spontaneous erections, loss of body hair and reduced need for shaving, gynaecomastia, and increased risk of osteoporosis or fracture.**
- **Biochemical evaluation should include measurement of circulating testosterone and luteinising hormone levels.**
- **Low testosterone levels are associated with increased risk of cardiovascular disease and increased mortality in ageing men. In this context, it remains unclear whether a reduced testosterone level is a causal factor or a biomarker for ill health.**
- **Adequately powered randomised clinical trials investigating testosterone therapy in older men with hard clinical endpoints are needed.**
- **Consensus clinical guidelines currently recommend making a diagnosis of androgen deficiency only in symptomatic men with unequivocally low testosterone levels, with a careful discussion of the risks versus benefits of any intervention.**

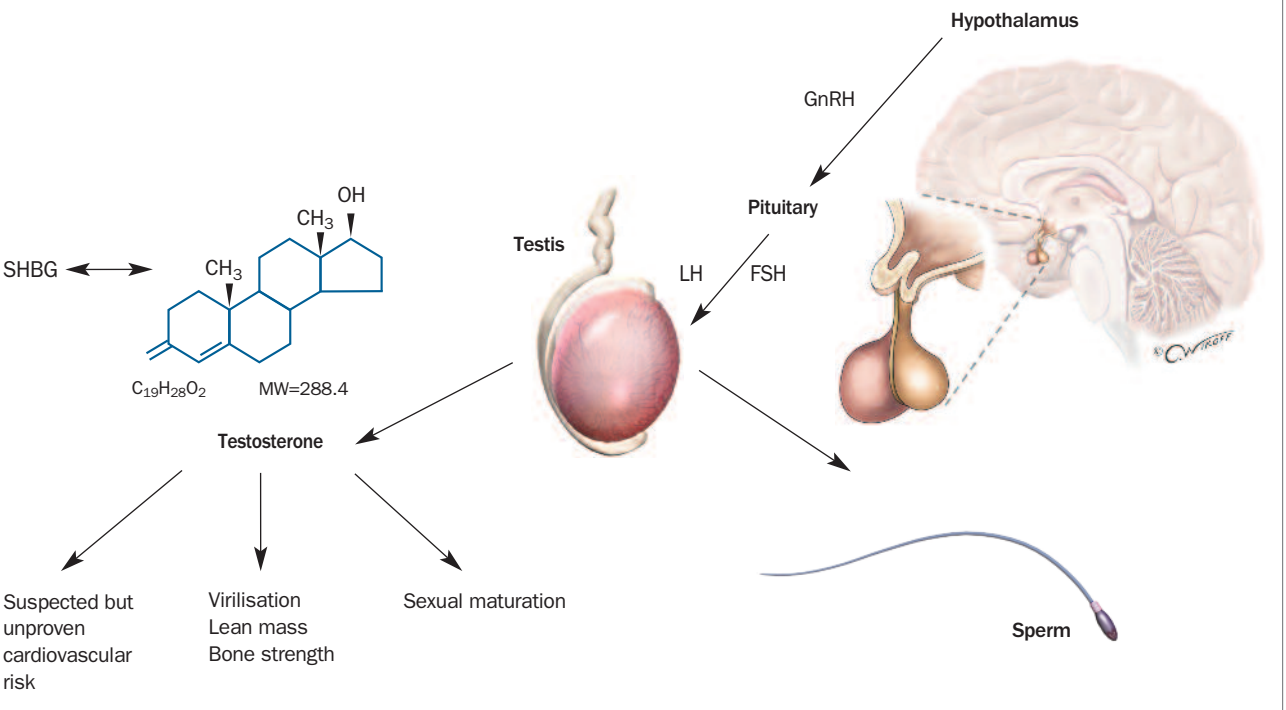

Figure. The hypothalamo-pituitary-gonadal axis and actions of testosterone.
ABBREVIATIONS: FSH = follicle-stimulating hormone; GnRH = gonadotrophin-releasing hormone; LH = luteinising hormone; SHBG = sex hormone-binding globulin.

Men with pathologically based hypogonadism who have an identifiable disruption of the hypothalamo-pituitary-gonadal axis and symptoms and signs strongly suggestive of androgen deficiency, qualify for subsidised therapy via the PBS under the authority 'androgen deficiency in males with established pituitary or testicular disorders' (see below for more details).

Declining testosterone levels and increasing ill health in ageing men

As men grow older, testosterone levels decline.[3] The difference has been estimated as 1% lower per year of age. Therefore, the older the sample of men examined the greater the proportion at or below any given threshold of testosterone.

There is ongoing debate over whether lower testosterone levels are a consequence of ageing or result from the cumulative effect of behavioural, lifestyle or health-related factors.[4] A higher body mass index is associated with lower free and total testosterone levels.[5,6] In older men testosterone levels in the low-normal range are associated with poorer health outcomes.[3,7]

In the Western Australian Health In Men Study (HIMS) involving 3638 community-dwelling men aged 70 years or older, testosterone levels in the lowest quartile were associated with increased incidence of stroke or transient ischaemic attack independently of conventional risk factors for cardiovascular disease.[8] A lower testosterone level was also associated with the presence of abdominal aortic aneurysm, a predictor of mortality from rupture or cardiovascular disease.[9] The HIMS and other studies have shown associations of low testosterone levels with increased risk of mortality.[10,11] However, there are no randomised controlled clinical trials of testosterone with the endpoint of incident cardiovascular events or mortality.[12] Such studies are difficult logistically because large numbers of men would need to be randomised and followed for an extended period of time to accumulate sufficient outcome events. Until such evidence is available, prescribing of testosterone therapy should be limited to men with proven androgen deficiency.[1,12]

'There is ongoing debate over whether lower testosterone levels are a consequence of ageing or result from the cumulative effect of behavioural, lifestyle or health-related factors'

Defining low testosterone levels

Currently the PBS allows consideration of testosterone therapy for 'androgen deficiency in males 40 years and older who do not have established pituitary or testicular disorders other than aging', with androgen deficiency confirmed by at least two testosterone levels of less than 8 nmol/L from blood samples taken on different mornings (see the full Schedule). Under these criteria therapy can also be considered for men with intermediate testosterone levels and high LH levels.

In community-dwelling older men serum testosterone is a continuous variable approximating the normal distribution.[5] It is therefore difficult to define a specific threshold as demarcating with sensitivity and specificity for 'low' testosterone levels in ageing men. Thresholds of 6.9, 9.8 or 10.4 nmol/L have been suggested, the latter two based on results in healthy younger men.[1,12,13] If the PBS threshold of less than 8 nmol/L is followed, then 5.2% of the 3638 men aged 70 to 89 years in HIMS would have had early morning testosterone levels below this level, albeit measured by immunoassay.[5] By comparison, 4.1% of 3369 men aged 40 to 79 years from the European Male Aging Study (EMAS) had testosterone levels below 8 nmol/L, measured using mass spectrometry.[14] However, fewer men in EMAS had symptoms consistent with androgen deficiency, as well as reduced testosterone levels.[14] Therefore, in the absence of pathologically based hypogonadism, only a minority of middle-aged and older men in the community would have testosterone levels low enough to warrant consideration of therapy.

Benefits of testosterone therapy

A meta-analysis of 29 randomised controlled trials involving 1083 men with a mean age of 64.5 years and baseline testosterone levels of 10.9 nmol/L indicated that the effects of testosterone therapy reduced total body fat (-1.6 kg), increased fat free mass (+1.6 kg) and increased bone mineral density (approximately 3% at lumbar spine) compared with placebo.[15]

A meta-analysis of 17 randomised placebo-controlled trials including 656 men aged 57.5 years with average testosterone levels at baseline of less than 12 nmol/L showed modestly improved sexual thoughts and motivation, frequency of successful intercourse and overall sexual satisfaction.[16] However, testosterone is less likely to improve symptoms of erectile dysfunction in men with predominantly neurovascular pathology.[17]

A placebo-controlled randomised trial of transdermal testosterone (50 mg/day) in 274 men aged 65 years or above with total testosterone levels of 12 nmol/L or less who were intermediate-frail or frail demonstrated an improvement in lower limb muscle strength over six months.[18] However, the benefit was not maintained at six months after cessation of therapy.[19]

Controversy following the TOM trial

Of note, the Testosterone in Older Men with Mobility Limitations (TOM) trial was a randomised, placebo-controlled trial investigating transdermal testosterone in men aged 65 years or above with a total testosterone level of 3.5 to 12.1 nmol/L and evidence of mobility limitation.[20] Therapy was started at a dose of 100 mg/day and titrated to maintain total testosterone levels in the range of 17.4 to 34.7 nmol/L. The trial was discontinued early because of a significantly higher incidence of adverse cardiovascular events in the testosterone group compared with placebo.[20] Therefore, caution is needed when considering more frail older men for testosterone therapy, and high doses of testosterone therapy are best avoided.

Screening and monitoring of patients on testosterone therapy

Consensus guidelines recommend pre-treatment screening of patients for prostate neoplasia, polycythaemia and obstructive sleep apnoea, and on-treatment monitoring of prostate-specific antigen, haematocrit and lipid profiles.[1] There are contrasting observational data with a large meta-analysis finding no association of endogenous testosterone levels with risk of prostate cancer,[21] but a recent epidemiological study has reported a possible association.[22]

A recent review of 51 interventional studies reported that testosterone therapy was associated with an increase in haemoglobin and haematocrit levels, and a decrease in HDL-cholesterol levels, with no significant effect reported for incidence of prostate cancer, cardiovascular outcomes or mortality.[23]

Efficacy of testosterone therapy can be gauged by symptomatic improvement, alterations in body composition and bone mineral density, and monitoring testosterone levels. However, long-term outcomes, optimal duration of treatment and risks of sustained therapy require clarification in adequately powered randomised controlled trials of extended duration.

Role of the GP

GPs play an important role in the initial assessment of patients with hypogonadism. Men presenting with symptoms suggestive of androgen deficiency should be carefully assessed because symptoms can be nonspecific.[1,12] Chronic disease, systemic illness or other factors known to be associated with low testosterone levels, such as obesity and use of alcohol, glucocorticoids, opiates or recreational drugs, need to be identified. Blood sampling for testosterone should be conducted early in the morning with use of an accurate assay.

Treatment should be directed at any underlying illness or condition predisposing to low testosterone levels. Men with testosterone levels in the normal range can be reassured that supplementation is not warranted. If pathologically based hypogonadism is present, testosterone supplementation can be considered. In older men without pituitary or testicular disease who have convincing symptoms and signs of androgen deficiency, the PBS criteria can be used as a threshold for classifying 'low' testosterone levels. The benefits versus risks of testosterone therapy need to be considered and discussed in an individual context for an informed decision to be made. Referral of patients to an endocrinologist is justifiable if there is doubt over the diagnosis of androgen deficiency or uncertainty regarding the optimal management plan.

Conclusion

Men with pathologically based hypogonadism merit evaluation for testosterone therapy. In the absence of pituitary or testicular disease, older men with symptoms and signs of androgen deficiency and confirmed low testosterone levels may be considered for testosterone supplementation. However, any decision to treat must be based on informed consent following careful discussion of benefits and risks of testosterone supplementation, acknowledging the incomplete evidence base. Men with normal testosterone levels should be discouraged from seeking hormonal therapy. **ET**

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